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Acute Effects of Subcutaneous Injection of Glucagon and/or Oral Administration of Glycerol on Blood Metabolites and Hormones of Holstein Dairy Cows Affected with Fatty Liver Disease

A.S. Leaflet R2090

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Summary

To study the effects of the subcutaneous injection of glucagon and/or oral administration of glycerol on blood metabolites and hormones of Holstein dairy cows induced with fatty liver disease, twenty multiparous cows were fed a dry cow ration supplemented with 12 kg of cracked corn during the dry period to increase the likelihood of fatty liver disease development. Cows with a body condition score (BCS) of ≥ 3.5 points (0-5 scale) were randomly assigned to one of four treatment groups--saline, glucagon, glucagon plus glycerol, and glycerol. Following treatment, serial blood samples were collected to determine the effect of glucagon and/or glycerol on blood composition. Glucagon injection alone increased postpartal plasma glucose, glucagon, and insulin and decreased plasma NEFA and TAG. Glucagon plus glycerol treatment increased and sustained postpartal plasma glucose and insulin and decreased postpartal plasma NEFA and TAG. Administration of glycerol alone increased plasma glucose and decreased plasma NEFA during the postpartal period. Early postpartal treatment of cows with glucagon and/or glycerol increased plasma glucose and decreased plasma NEFA. This response would suggest that these treatments would decrease the likelihood of fatty liver disease in dairy cows.

Introduction

Dairy cows that are obese or over-conditioned during the periparturient period are susceptible to a complex of metabolic and infectious diseases known as fat cow syndrome. Fat cow syndrome is well known to commence as fatty liver disease (FLD) before it exacerbates to other interrelated metabolic disorders such as ketosis and milk fever (decreased plasma calcium). Infectious sequelae to fatty liver disease include mastitis and metritis often associated with retained placenta. Other complications commonly seen with disease include left displaced abomasum and laminitis.

Fatty liver disease affects cows in the late prepartal (1 wk before calving) and early postpartal periods (up to 2 wk

after calving). The severity of FLD is often classified on the basis of the percentage of accumulated triacylglycerol (TAG) in the liver to assess the potential for deleterious effects to the health, productivity (kg of milk), and reproductivity of dairy cows.

Extensive studies have been undertaken to unravel the etiology of fatty liver disease as the underlying cause of fat cow syndrome. During the final weeks that immediately preceding parturition, feed intake progressively decreases to about 30% of normal on the day of parturition. This sharp decrease in feed intake is accompanied with an increased periparturient energy requirement to facilitate colostrum production. This results in a negative energy balance. To accommodate this energy deficit, it is essential for the cow to mobilize body fat reserves. Lipolysis is upregulated and nonesterified fatty acids (NEFA) from adipose tissue overwhelm the liver. Part of NEFA is esterified to be converted into triacylglycerol (TAG) that accumulate in the liver, causing fatty liver disease symptoms. It has been hypothesized that finding a preventative for fatty liver will likely prevent other interrelated metabolic disorders and infectious diseases during the peripartal (around calving) period.

Cows suffering fatty liver are treated similarly to cows affected with ketosis. In mild cases, they are treated with oral glucose precursors such as propylene glycol. In extreme cases, they are treated with intravenous dextrose infusions accompanied by intramuscular glucocorticoid injections. As a preventative against fatty liver disease and ketosis, glycerol mixed with feed has been evaluated. Glycerol drenches also have been assessed to alleviate ketosis.

Therapy of FLD is frustrating and rarely effective. A member of our research group recently demonstrated that continuous intravenous infusion of glucagon is efficacious in alleviating the fatty liver-ketosis complex in Holstein dairy cows. Nonetheless, intravenous injection is considered impractical in a dairy farm setting. It was subsequently demonstrated that subcutaneous injections of glucagon starting at d 8 postpartum alleviated fatty liver-ketosis complex symptoms from experimentally affected cows. More recently, we have shown that subcutaneous glucagon injections on d (1) prevent development of ketosis. The biochemical basis by which glucagon and/or glycerol exert their preventative action, however, is not fully understood. The objective of this study was to understand the biochemical basis by which glucagon and/or glycerol prevent fatty liver disease.

The ultimate goal of this study is to provide the U.S. farmers with a slow-release subcutaneous implant of

glucagon and/or a glycerol feeding protocol as an effective tool for treating fatty liver disease in dairy cows.

Materials and Methods

Twenty multiparous (more than 2 calves) Holstein dairy cows with BCS of 3.5 or better were selected during the dry period. Cows were randomly assigned to one of four treatment groups that received the following treatments:

1. Control group: Cows (n=4), starting at 6:00 h on d (1) postpartum (after calving), received 60 mL of saline (pH 10.25) subcutaneously at 8 h intervals for 14 days.

2. Glucagon group: Cows (n=4), starting at 6:00 h on d (1) postpartum, received 5 mg of glucagon dissolved in 60 mL of saline (pH = 10.25) subcutaneously at 8 h interval for 14 days and once on d (15) postpartum.

3. Glycerol group: Cows (n = 6), starting at 6:00 h on d (1) postpartum, received 500 mL of glycerol diluted with 100 mL of water orally once daily for 14 days.

4. Glucagon-glycerol group: Cows (n=6), starting at 6:00 h on d (1) postpartum, received 5 mg of glucagon dissolved in 60 mL of saline (pH=10.25) subcutaneously at 8 h intervals for 14 days and once on d (15) plus 500 mL of glycerol diluted with 100 mL of water once daily at 6:00 h.

Blood samples were collected on d (1), d (7), and d (13) postpartum (after calving) using a jugular catheter. Twenty milliliters of blood were collected into two tubes containing Na-EDTA at 15, 10, 5 min before administering each treatment and then at 15, 30, 45, 60, 80, 100, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min after treatment. Tubes were placed on ice until plasma was separated by centrifugation at 500 x g. Plasma was stored at -20°C for subsequent analyses.

Results and Discussion

We hypothesized that glucagon, glycerol, or glucagon plus glycerol could be administered to early postpartal cows to alleviate or prevent fatty liver disease. This clinical action is likely achieved by improving the energy status of the affected dairy cow. Our results have corroborated this hypothesis.

Glucagon, glycerol, and glucagon plus glycerol treatments increased plasma glucose concentration (figures 1, 2, and 3). Glucagon plus glycerol treatment dramatically increased plasma glucose concentrations 50 % on d (1), d (7), and d (13) postpartum by more than 40 mg/dL greater than that of the control group and maintained it at an elevated concentration for longer time than did other treatments (figures 1 and 3). Glucagon treatment did not affect plasma NEFA concentration on d (1), but it did on d (7) and d (13) (figures 4, 5, and 6). Glucagon plus glycerol decreased plasma NEFA concentrations and maintained lower NEFA for longer time than other treatments on d (1) postpartum. Plasma NEFA concentration, however, was decreased by glucagon plus glycerol and glycerol treatments on all three sampling days. Glycerol treatment maintained plasma NEFA low for longer time than did glucagon plus

glycerol treatment on d (7) and (13) postpartum (figures 5 and 6).

Glucagon is a potent glycogenolytic hormone that activates glycogen phosphorylase that causes glycogen to release glucose. Glucagon also increases gluconeogenesis by increasing liver uptake of amino acids that are used as a glucose precursor and thus further increase plasma glucose and by increasing the concentration of rate-limiting gluconeogenesis enzymes.

Glycerol is an efficient glucogenic substrate (can be converted to glucose) because it enters the gluconeogenesis pathway at the triose phosphate level; glycerol, therefore, is not affected by the rate-limiting enzymes phosphoenolpyruvate carboxykinase and pyruvate carboxylase. Glycerol can increase plasma glucose in the absence of propionate coming from rumen fermentation at time of decreased feed intake.

Glucagon treatment increased plasma glucagon concentration (figure 7, 8, and 9). Also, glucagon treatment increased plasma insulin on d (7) and d (13) postpartum but only slightly on d (1) (figures 10, 11 and 12).

Glucagon, glycerol, and glucagon plus glycerol increased plasma glucose. This response necessitates plasma insulin to increase. The increase in plasma insulin is an essential signal that indicates energy abundance. Insulin activates glucose uptake and storage by muscles and adipose tissues (lipogenesis). Insulin also stimulates ion uptake such as K^{+} and PO_4^{-3} and amino acid uptake and protein synthesis. Insulin also is needed to restrain metabolic processes that release stored body energy such as lipolysis, ketogenesis, and glycogenolysis. All of these responses suggest that glucagon, glycerol, and glucagon plus glycerol stimulate insulin release that could, in part, cause the metabolic responses that prevent the development of fatty liver by glucagon as shown in earlier research.

Conclusion

Glucagon, glycerol, and glucagon plus glycerol decreased plasma NEFA concentration and increased plasma glucose. Glucagon treatment also elevated plasma insulin concentration. These metabolic responses may explain why glucagon treatment in previous research decreased fatty liver development.

Acknowledgement

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Plasma glucose d (1)

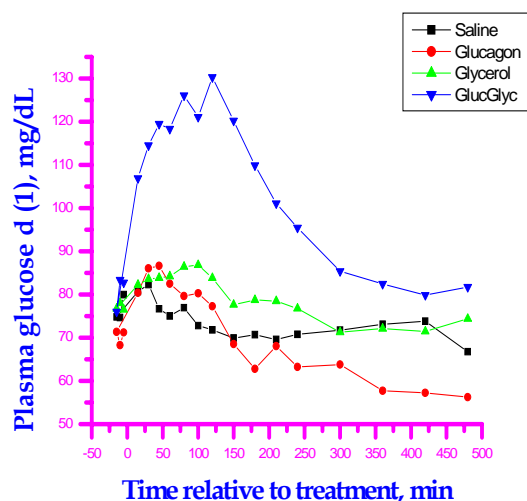


Figure 1. Effect of treatments on plasma glucose concentration on d (1) postpartum. Glucagon, glycerol, and glucagon plus glycerol (greatest stimulus) treatments increased plasma glucose.

Plasma glucose d (13)

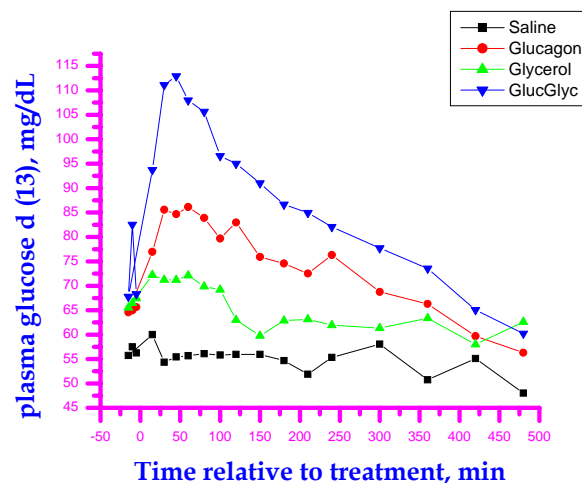


Figure 3. Effect of treatments on plasma glucose concentration on d (13) postpartum. Glucagon, glycerol, glucagon plus glycerol increased plasma glucose.

Plasma glucose d (7)

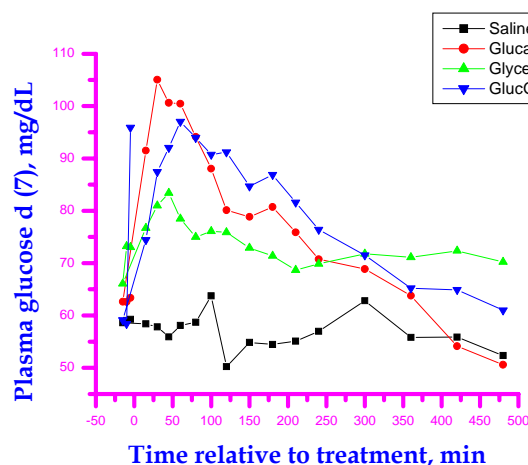


Figure 2. Effect of treatments on plasma glucose concentration on d (7) postpartum. Glucagon, glycerol, and glucagon plus glycerol increased plasma glucose.

Plasma NEFA d (1)

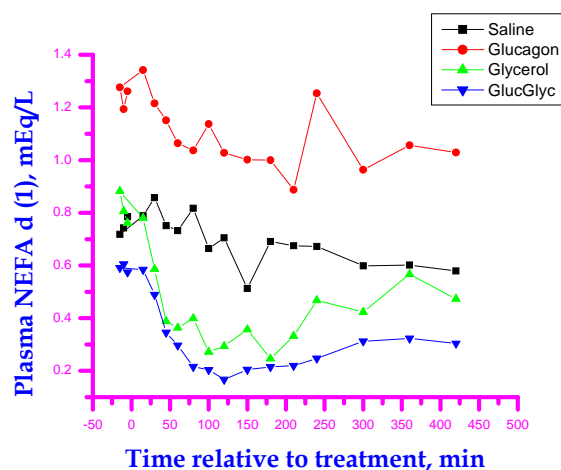


Figure 4. Effect of treatments on plasma NEFA concentration on d (1) postpartum. Glucagon, glycerol, glucagon plus glycerol decreased plasma NEFA.

Plasma NEFA d (7)

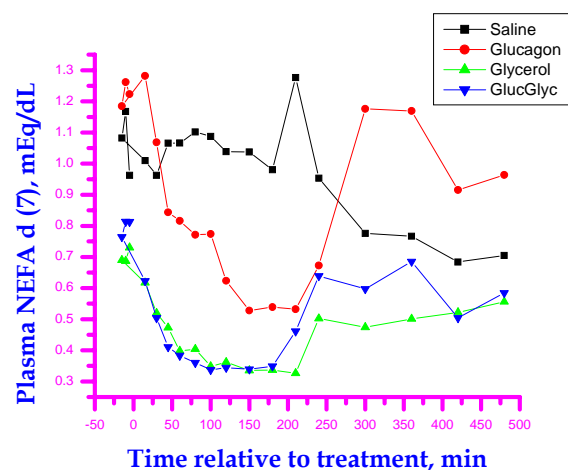


Figure 5. Effect of treatments on plasma NEFA concentration on d (7) postpartum. Glucagon, glycerol, and glucagon plus glycerol decreased plasma NEFA.

Plasma glucagon d (1)

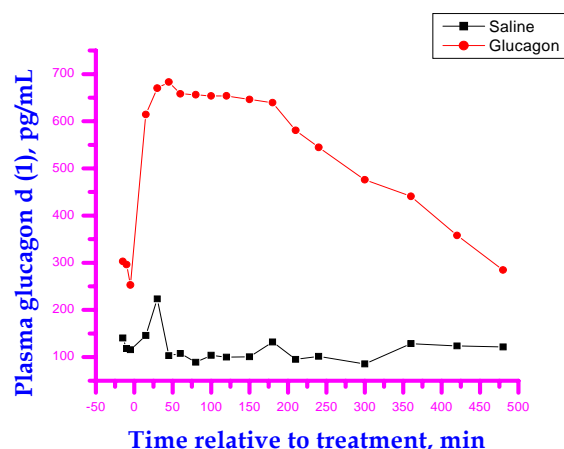


Figure 7. Effect of glucagon treatment on plasma glucagon concentration on d (1) postpartum. Glucagon treatment increased plasma glucagon.

Plasma NEFA d (13)

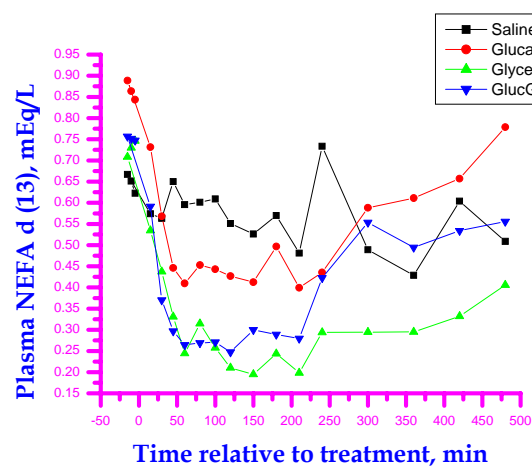


Figure 6. Effect of treatments on plasma NEFA concentration on d (13) postpartum. Glucagon, glycerol, and glucagon plus glycerol decreased plasma NEFA.

Plasma glucagon d (7)

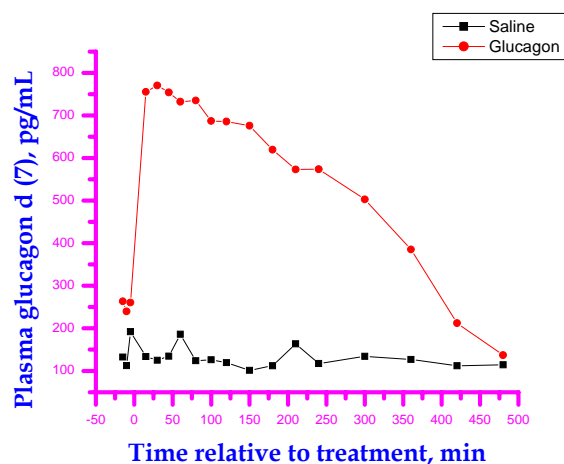


Figure 8. Effect of glucagon treatment on plasma glucagon concentration on d (7) postpartum. Glucagon treatment increased plasma glucagon concentration

Plasma glucagon d (13)

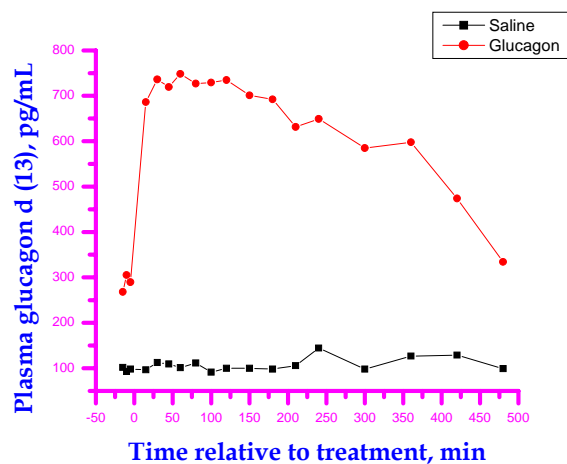


Figure 9. Effect of glucagon treatment on plasma glucagon concentration on d (13) postpartum. Glucagon treatment increased plasma glucagon.

Plasma insulin d (7)

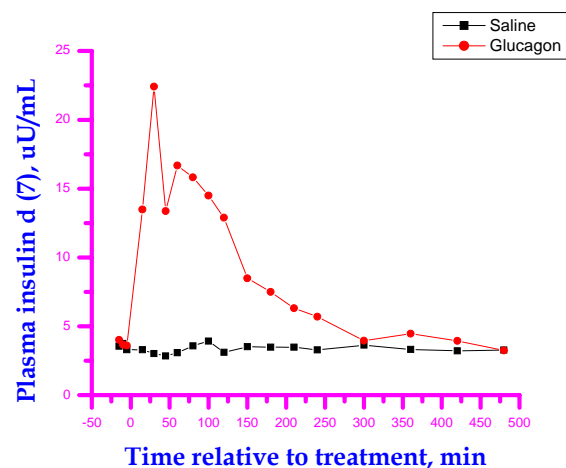


Figure 11. Effect of glucagon treatment on plasma insulin concentration on d (7) postpartum. Glucagon increased plasma insulin.

Plasma insulin d (1)

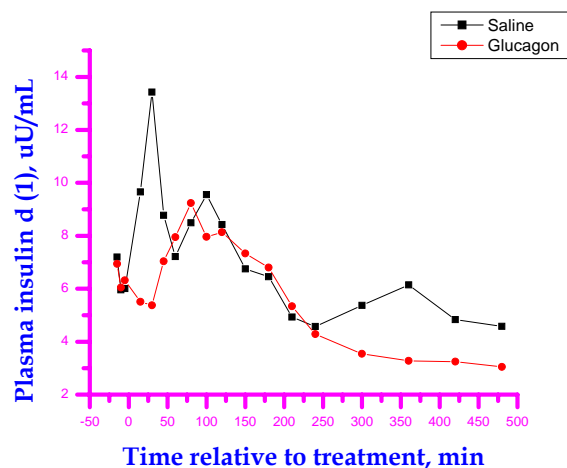


Figure 10. Effect of glucagon treatment on plasma insulin concentration on d (1) postpartum. Glucagon increased plasma insulin.

Plasma insulin d (13)

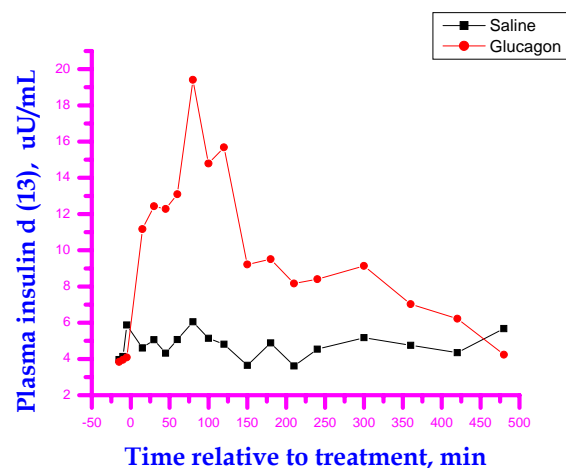


Figure 12. Effect of glucagon treatment on plasma insulin concentration on d (13) postpartum. Glucagon increased plasma insulin.